TRANSLATION

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
347171/D21706		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/FR2004/003397	28.12.2004	30.12.2003
International Patent Classification (IPC) or national classification and IPC		
C07H21/00 C12N15/11		
Applicant		
L V M H RECHERCHE		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:

      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/EP	Authorized officer
Facsimile No.	Telephone No.

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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages 1-30 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ the claims:

nos. _____ as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* 1-18 received by this Authority on 29.05.2006 with telefax

nos.* _____ received by this Authority on _____

☐ the drawings:

sheets _____ as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☒ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☒ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☒ the claims, nos. 19-21

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

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Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	16, 17	YES
	Claims	1-15, 18	NO
Inventive step (IS)	Claims		YES
	Claims	1-18	NO
Industrial applicability (IA)	Claims	1-18	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

1. Reference is made to the following documents:

D1: WO 95/02069 A (BENNETT C FRANK; BOGGS RUSSELL T (US); DEAN NICHOLAS M (US); ISIS PHA) 19 January 1995 (1995-01-19)

D2: PARK H-Y ET AL: "THE BETA ISOFORM OF PROTEIN KINASE C STIMULATES HUMAN MELANOGENESIS BY ACTIVATING TYROSINASE IN PIGMENT CELLS" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 268, no. 16, 5 June 1993 (1993-06-05), pages 11742-11749, XP002036373 ISSN: 0021-9258

D3: NISHIZUKA Y: "THE MOLECULAR HETEROGENEITY OF PROTEIN KINASE C AND ITS IMPLICATIONS FOR CELLULAR REGULATION" NATURE, NATURE PUBLISHING GROUP, LONDON, GB, vol. 334, 25 August 1988 (1988-08-25), pages 661-665, XP001118326 ISSN: 0028-0836

D4: PARK H-Y ET AL: "The receptor for activated C-kinase-1 (RACK-I) anchors activated PKC-β on melanosomes", J. of Cell Science, 117(16), July 2004, 3659-3668, published after the priority date and cited by the applicant.

D5: PARK H-Y ET AL: "Topical Application of a protein kinase C inhibitor reduces skin and hair

pigmentation", J. Invest Dermatol., 122:159-166, Jan. 2004, published after the priority date and cited by the applicant.

2. Claims 1 to 15 and 18

The present application fails to meet the requirements of PCT Article 33(1), since the subject matter of claims 1 to 15 and 18 does not comply with the criterion of novelty as defined by PCT Article 33(2). Moreover, the subject matter of said claims relates to a topical pharmaceutical composition including an oligonucleotide capable of hybridising specifically with PKC-beta-1 genes.

D1 describes (see pages 25 to 26) antisense oligonucleotides enabling specific hybridisation with the genes or messenger RNA coding for the protein PKC-beta 1, so as to modulate the expression thereof, and, more particularly, oligonucleotides having sequences identical to those of the present claim 3 (see the table: SEQ.ID N°25 of D1 = SEQ.ID N°2; SEQ.ID N°26 of D1 = SEQ.ID N°3; SEQ.ID N°27 of D1 = SEQ.ID N°4; SEQ.ID N°28 of D1 = SEQ.ID N°1; SEQ.ID N°29 of D1 = SEQ.ID N°5). Said oligonucleotides can also be modified (see claims 3 to 13 of D1).

Furthermore, D1 claims the pharmaceutical compositions containing said oligonucleotides (see claim 36) and more particularly the topical formulations (see page 18, lines 6 to 19).

Hence, D1 entirely anticipates the subject matter of claims 1 to 15 and 18 of the present application.

However, the use of such oligonucleotides for preparing a topical pharmaceutical composition for treating or preventing regional hyperpigmentations caused by melanocyte hyperactivity, as claimed in the original claim 20 is to be considered novel over D1.

3. Claims 16 to 17

The oligonucleotides described in D1 are specific to the various isoforms of the protein PKC and enable the role of these various isozymes to be assessed, hence they can be used in the treatment of illnesses associated with these specific isozymes, such as inflammations and hyperproliferative disorders. However, D1 does not mention the specific role played in melanogenesis by the beta-1 isoform of the protein kinase C.

The subject matter of claims 16 and 17, which relate respectively to cosmetic compositions containing the oligonucleotides according to claims 1 to 15 and the use thereof as an inhibitor of melanine synthesis for depigmenting or bleaching the skin or hair, is novel over D1.

However, the present application fails to meet the requirements of PCT Article 33(1), since the subject matter of claims 16 and 17 does not involve an inventive step as defined by PCT Article 33(3).

D2, which is considered to be the closest prior art, describes the role as an activator of tyrosinase by phosphorylation played by PKC and the key role of

tyrosinase in melanogenesis, and assesses the functions of each of the isoforms of PKC according to the cell types and explicitly indicates that skin pigmentation is directly associated with the beta isoform of the protein kinase C. D2 therefore explicitly describes the role of PKC-beta in melanogenesis (see abstract). Consequently, the subject matter of claims 16 and 17 of the present application differs from D2 only in that it refers to the **beta 1 isoform** of PKC and the specific role thereof in **melanogenesis**.

Apart from the fact that D4 and D5 were published after the priority date of the present application, contrary to the applicant's assertions, specific inhibitors of the various isoforms of the protein kinase C are known from the prior art, particularly from D1. Furthermore, referring to D4, page 3660, left-hand column, fourth paragraph, the applicant is of the opinion that it follows therefrom that PKC β2 is specifically involved in the stimulation of melanogenesis. However, according to D4, this information is derived ("Therefore, PKC-β2 is specifically implicated in…") from transfection studies performed on human NP-melanocytes with cDNA of PKC-βII showing the activation of tyrosinase as described in the document "Park et al., 1993" (see D4, preceding sentence). According to the references of D4, said document "Park et al., 1993" is indeed D2, which, contrary to the assertions of D4, does not mention at any point the role played by the **isoform βII** as a tyrosinase activator in melanogenesis. D2 merely indicates the specific role of the beta isoform of PKC in melanogenesis, without investigating further types 1

and/or 2 of this isoform.

At the priority date of the present application and in the light of D2, which is considered to be the closest prior art, the problem that the present invention is intended to solve can therefore be considered to be that of obtaining inhibitors of PKC β proteins, capable of blocking the activation of tyrosinase in melanogenesis, for depigmenting or bleaching the skin.

The solution proposed in claims 16 and 17 of the present claim is not considered inventive (PCT Article 33(3)) for the following reasons;

The various isoforms α, β_I, β_{II}, ζ, δ, Y and ε of PKC are known from the prior art (see for example D1 and D3) and the inhibitors thereof or even the specific antisense oligonucleotides of each of said isoforms, particularly beta and more particularly beta 1 or beta 2, are also known from D1 (see pages 26 to 27, tables 2 to 4) so as to modulate the specific expression of each of said genes.
Thus, in the light of D1, it is obvious for a person skilled in the art seeking to solve the stated problem to apply these antisense oligonucleotides known from tables 2 to 4 of D1 in routine hybridisation studies so as to assess the inhibiting activity and the specificity of each of said beta isoforms in melanogenesis, as taught in D2, and thereby obtain the features according to claims 16 and 17 without exercising inventive skill.

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Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment* on _____

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

The sequence listing in the description pages 1,2 as originally filed.

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*